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ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/589,116	SOREQ ET AL.	
	Examiner	Art Unit	
	SUZANNE M. NOAKES	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-41* is/are pending in the application.

4a) Of the above claim(s) *26-33 and 38-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08/11/2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *0619/08 & 07/07/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group II, claims 34-37 and the species chronic stress in the reply filed on 28 September 2009 is acknowledged.

Status of the Claims

2. Claims 26-41 are pending; Claims 26-33 and 38-41 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Claims 34-37 are subject to examination on the merits.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on 07 July 2008 and 19 June 2008 have been considered by the examiner. See initialed and signed PTO-1449.

Drawings/Specification

Compliance with Sequence Rules

4. The sequence listing, filed in computer readable form (CRF) and paper copy on 11 August 2006, has been received and entered. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to **fully** comply with the requirements of 37 C.F.R. § 1.821 through 1.825;

Applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990).

The following Figures contain sequences that contain four or more consecutive amino acids without any corresponding SEQ ID NO: and/or no reference to any SEQ ID NO: in the Brief Description of the Drawings.

a) In Figure 1A and Figure 1B, show C-terminal amino acid sequences of AChE-S and AChE-R without SEQ ID NO identification.

* If the noted sequences are in the sequence listing as filed, Applicants must amend the specification to identify the sequences appropriately by SEQ ID NO. If the noted sequences are not in the sequence listing as filed, Applicants must provide (1) a substitute copy of the sequence listing in both computer readable form (CRF) and paper copy, (2) an amendment directing its entry into the specification, (3) a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. § 1.821 (e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d), and (4) any amendment to the specification to identify the sequences appropriately by SEQ ID NO.

5. The disclosure is objected to because of the following informalities: the sequence identifiers should be in the preferred format of "SEQ ID NO:" rather than 'SEQ. ID. NO.' as used throughout the specification.

Appropriate correction is required.

Claim Objections

6. Claims 34 and 37 are objected to because of the following informalities: sequence identifiers should be in the preferred format of "SEQ ID NO:" rather than 'SEQ. ID. NO.'.

7. Claims 34-37 are objected to because in the first instance where an acronym is used in an independent claim, said acronym should be spelled out in full, followed by the abbreviation in parenthesis. Thus, "AChE" should be spelled out as 'acetylcholinesterase (AChE)'.

Appropriate correction is required.

Claim Rejections - 35 USC § 112 – 2nd paragraph

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 34 and 37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim Rejections - 35 USC § 112 – 1st paragraph

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claim 34 and 37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claim is drawn to a method of ***preventing*** or treating conditions wherein lymphocyte activity is reduced by administering a therapeutically effective amount of an AChE-derived peptide of SEQ ID NO: 1, functional fragments or derivatives thereof to a subject in need thereof. Thus, the claim is suggesting that complete inhibition or prevention of such diseases as any autoimmune disease, inflammation, rheumatoid arthritis, multiple sclerosis, chronic stress etc. can be prevented by administering said AChE-derived peptide; however, complete prophylaxis of such diseases is a standard that is unachievable and the specification, while suggesting treatment of said conditions might be possible, does not describe prevention

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir.1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to

practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the relative skill of those in the art, (5) the predictability or unpredictability of the art, (6) the amount or direction or guidance presented, (7) the presence or absence of working examples, and (8) the quantity of experimentation necessary.

Although the quantity of experimentation alone is not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a fledgling art that is unpredictable where no guidance or working examples are provided in the specification and prior art, whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working example or the experimentation required is in a predictable established art. Conversely, a large quantity of experimentation would require a correspondingly greater quantum of guidance, predictability and skill in the art to overcome classification as undue experimentation. In Wands, the determination that undue experimentation was not required to make the claimed invention was based primarily on the nature of the art, and

the probability that the required experimentation would result in successfully obtaining the claimed invention. (Wands, 8 USPQ2d 1406). Thus, a combination of factors which, when viewed together, would provide an artisan of ordinary skill in the art with an expectation of successfully obtaining the claimed invention with additional experimentation would preclude the classification of that experimentation as undue. A combination of Wands factors, which provide a very low likelihood of successfully obtaining the claimed invention with additional experimentation, however, would render the additional experimentation undue.

1.Breadth of the claims.

In regards to the method of the invention and the breadth of the claims the broadest interpretation that applies is a method of preventing chronic stress (and autoimmune diseases, inflammation, rheumatoid arthritis, MS, amyotrophic lateral sclerosis, fibromyalgia, multiple chemical sensitivity, post-irradiation chemotherapy in subjects in need thereof.

2. The nature of the invention.

The invention is designed to provide a way to inhibit chronic stress (and autoimmune diseases, inflammation, rheumatoid arthritis, MS, amyotrophic lateral sclerosis, fibromyalgia, multiple chemical sensitivity, post-irradiation chemotherapy, from occurring to those that are susceptible. This would mean that said conditions have been determined to exist previous to the administration of the AChE-derived peptide.

3. The state of prior art.

In regards to the treatment of chronic stress (and autoimmune diseases, inflammation, rheumatoid arthritis, MS, amyotrophic lateral sclerosis, fibromyalgia, multiple chemical sensitivity, post-irradiation chemotherapy, the prior art provides evidence for the treatment using various peptides, proteins, antibodies, etc. However, a method of **prevention** of any of these conditions is not disclosed in the previous studies of such topic.

4. The relative skill in the art.

The relative skill in the art as it relates to the method of the invention is characterized by that of a M.D. or Ph. D. level individual.

5. The level of predictability in the art.

Since there is not much known about the nature of preventing any of these conditions the specification would need to have more detail as how to make and use the invention. One skilled in the art would not be able to readily anticipate the effect of administering the AChE-derived peptides of the current invention in regards to preventing all of the noted conditions. Certainly said administration may help to treat said conditions it, but there will always be a patient population that will get any or all of these conditions despite the administration of AChE-derived peptides because the exact causes of MS for example, is not known. The other conditions have a multitude of contributing factors as well making it significantly complex.

6. The amount of guidance present.

The applicant has not provided any guidance for the absolute prevention conditions wherein lymphocyte activity is reduced such as chronic stress (and autoimmune diseases, inflammation, rheumatoid arthritis, MS, amyotrophic lateral sclerosis, fibromyalgia, multiple chemical sensitivity, post-irradiation chemotherapy.

7. The existence of working examples.

The specification does not provide any information or examples that would suggest that Applicants invention can be used to completely prevent conditions wherein lymphocyte activity is reduced such as chronic stress (and autoimmune diseases, inflammation, rheumatoid arthritis, MS, amyotrophic lateral sclerosis, fibromyalgia, multiple chemical sensitivity, post-irradiation chemotherapy.

8. The quantity of experimentation necessary.

The quantify of experimentation would be significant because it would require testing large patient populations to see if prevention occurred all of the time in all populations for all of the noted conditions.

Due to the large quantity of experimentation necessary to provide evidence that the claimed administration of AchE-derived peptides of the invention will prevent conditions wherein lymphocyte activity is reduced such as chronic stress (and autoimmune diseases, inflammation, rheumatoid arthritis, MS, amyotrophic lateral sclerosis, fibromyalgia, multiple chemical sensitivity, post-irradiation chemotherapy, the lack of guidance presented in the specification regarding the same, the absence of a working example directed to same, the unpredictable nature of the invention with regards to prevention, the state of the prior art not providing any evidence for any

methods of prevention for conditions wherein lymphocyte activity is reduced such as chronic stress (and autoimmune diseases, inflammation, rheumatoid arthritis, MS, amyotrophic lateral sclerosis, fibromyalgia, multiple chemical sensitivity, post-irradiation chemotherapy, and the breadth of the claims which fails to provide particular steps involved in the prevention of conditions wherein lymphocyte activity is reduced such as chronic stress and autoimmune diseases, inflammation, rheumatoid arthritis, MS, amyotrophic lateral sclerosis, fibromyalgia, multiple chemical sensitivity, post-irradiation chemotherapy, the specification fails to teach the skilled artisan in the art how to make and use the invention.

12. Claim 37 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claim is drawn to a method of treating a condition wherein lymphocyte activity is reduced wherein said condition is exemplified (selected from a group consisting of?) chronic stress and autoimmune diseases, inflammation, rheumatoid arthritis, MS, amyotrophic lateral sclerosis, fibromyalgia, multiple chemical sensitivity, post-irradiation chemotherapy by obtaining blood from said subject, isolating immature cells and contacting said cells with an AChE-derived peptide of SEQ ID NO: 1 or a functional fragment or derivative thereof. The claim is not deemed enabled for the following reasons. The simple removal of blood from a patient will not treat any of the

noted conditions. The claim reads and is interpreted to treat the noted conditions by simply removing blood from a subject. The subsequent steps of the method of isolating immature cells and contacting said cells will be completely irrelevant with regards to treating anything because said contacting is occurring *ex vivo* and thus will have no impact whatsoever on the noted conditions. Thus, without additional steps, there is no way that the claim as written will ever be capable for treating any condition such as chronic stress, autoimmune diseases, inflammation, rheumatoid arthritis, MS, amyotrophic lateral sclerosis, fibromyalgia, multiple chemical sensitivity, post-irradiation chemotherapy.

13. Claims 34 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating conditions wherein lymphocyte activity is reduced by administering a therapeutically effective amount of the AChE peptide of SEQ ID NO: 1, does not reasonably provide enablement for a method of treating conditions wherein lymphocyte activity is reduced by administering a therapeutically effective amount of the AChE peptide of SEQ ID NO: 1 or any functional fragments or derivatives thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir.1988) and described above.

In the instant case, the claims are drawn to methods of treating or preventing any sort of condition having reduced lymphocyte activity, such as chronic stress, autoimmune diseases, inflammation, rheumatoid arthritis, MS, amyotrophic lateral sclerosis, fibromyalgia, multiple chemical sensitivity, post-irradiation chemotherapy by administering SEQ ID NO: 1 or any functional fragment or derivative thereof. SEQ ID NO: 1 the C-terminal 26 amino acids of the acetylcholinesterase-R (AChE-R) also referred to in the specification as ARP_{26}. The specification, however, only utilizes this 26 amino acid peptide consisting of SEQ ID NO: 1. Nowhere in hte specification is it indicated what are the essential and non-essential amino acids and thus one skilled in the art must first ascertain this before being able to produce functional fragments and/or derivatives thereof, this of course be done before even attempting to utilize said peptides in the claimed methods. This is seen as undue experimentation because the problem of prediction protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success is limited. Certain positions in the sequence are critical to the protein's structure/function relationship, such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. Particular regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions as all (see Bowie et al. pp.

1306-10, specifically p. 1306 column 2, paragraph 2; Wells pp. 8509-8517). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the peptide which are tolerant to change (e.g. by amino acid substitutions or deletions or insertions), and the nature and extent of changes that can be made in these positions. The specification does not provide any guidance as to what are critical and non-critical residues which allow said peptide to function as required (e.g. by being able to treat the noted conditions) and thus is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon the surrounding residues; therefore substitution or non-essential residues can often destroy activity. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and screen the same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to the same, the complex nature of the invention, the state of the prior art which established the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would

be required of the skilled artisan to make and/or use the claimed invention in its full scope.

14. Claim 35 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inducing a shift in the activity of lymphocytes *in vitro* or *ex vivo* utilizing AChE-R or SEQ ID NO: 1, does not reasonably provide enablement for utilizing any AChE-derived peptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir.1988) and described above.

It is known in the prior art and recited in the specification that there are various forms of AChE derived peptides, e.g. those derived from AChE-R or AChE-S etc. However, the specification clearly describes that it is the C-terminal peptide of AChE-R that has the required activity of being able to interact and moderate the activity of lymphocytes. No other kind of AChE-derived peptide has been noted to possess this activity and nothing in the prior art suggests that any AChE full enzyme or peptide derived therefrom also possesses this activity. As such, ascertaining which peptides have the required function would be considered as undue experimentation is seen as undue. This is in part due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and screen the same for

activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to the same, the complex nature of the invention, the state of the prior art which established the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Written Description:

15. Claims 34, 35 and 37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to methods of treating or preventing conditions wherein lymphocyte activity is reduced such as in chronic stress, autoimmune diseases, inflammation, rheumatoid arthritis, MS, amyotrophic lateral sclerosis, fibromyalgia, multiple chemical sensitivity, post-irradiation chemotherapy by administering SEQ ID NO: 1 or any functional fragment or derivative thereof (Claim 34) or by isolating immature cells and contacting said cells with an AChE-derived peptide, or functional fragment or derivative there of SEQ ID NO: 1 (claim 37) or a method of inducing a shift in the activity of lymphocytes by contacting said lymphocytes (in vitro or ex vivo) with an

AChE-derived peptide. Thus, the methods are drawn to methods which utilize a genus of polypeptides in order to treat of prevent said conditions.

As noted above, the standard and requirement for prevention has not been met, e.g. while Applicants might be in possession for treatment, they have not described and are deemed not to be in possession of methods of preventing the noted conditions.

With regard to methods of treating utilizing a large and variable genus of peptides of SEQ ID NO: 1, functional fragments thereof and derivatives thereof, the specification describes a single species (e.g. SEQ ID NO: 1) which is representative of the entire diverse and variable genus which might be utilizable for treating said conditions. This, however, is not deemed representative of said genus.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, at the time the invention was made, of the specific subject matter claimed. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); *In re Gostelli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966." *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

MPEP § 2163 further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." Furthermore, the courts have also held that possession may not be shown by merely describing how to obtain possession of members of the claimed genus or how to identify their common structural features. *See University of Rochester*, 358 F.3d at 927, 69 USPQ2d at 1895. In addition, *In re Alonso*, 88 USPQ2d 1849 (Fed. Cir. 2008) established that a single species directed to a method of treating was not sufficient to claim the entire broad and variable genus. As such, the claims are deemed to lack written description for methods of treating and preventing utilizing the broad and variable genus of peptides claimed.

Claim Rejections - 35 USC § 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

17. Claim 34 is rejected under 35 U.S.C. 102(b) as being anticipated by Soreq et al. (US 2003/0036632 – cited on IDS of 07-70-2008).

The claim is drawn to a method of treating or preventing various conditions wherein lymphocyte acitivty is reduced by administering to a subject in need a therapeutically effective amount of SEQ ID NO: 1 (which is the C-terminal 26 amino acids of AChE-R/ARP_{26}).

Soreq et al. teach the following in Example 10, paragraph 0321:

> To determine the *in vivo* capacity of ARP to affect hematopoietic expansion under acute psychological trauma, mice were injected immediately after the stress protocol with 0.1 mg/kg ARP or 30 ng/kg AS1. Another group of mice were not subjected to stress and were injected intraperitoneally with normal saline (n=6) or ARP (n=4). 24 hours later, the animals were sacrificed and whole blood obtained for AChE activity and white blood cells. Bone marrow smears were subjected to immunohistochemical labeling with an affinity purified rabbit antiserum prepared against GST-fused recombinant ARP. FIG. 12B shows the number of labeled cells per 100 cells counted at .times.1000 magnification in 5 different fields. Bone-marrow labeling and white blood cell (WBC) count were similar in non-stressed mice regardless of ARP injection. In contrast, ARP intensified labeling and increased the number of small positive cells in the bone marrow of stressed mice, indicating that it enhances AChE expression and increases stem cell expansion in vivo. AS1 reduced the number of cells labeled with anti-ARP antibodies (FIG. 12B). In peripheral blood, WBC counts revealed similar ARP-dependent enhancement and AS1 suppression.

It is noted that paragraph 0195 of Soreq et al. define ARP as follows:

"[0195] ARP: 1-GMQGPAGSGWEEGSGSPPGVTPLFSP-26, also denoted as SEQ ID: No. 1."

Said SEQ ID NO: 1 of Soreq et al. is 100% identical to the instant SEQ ID NO: 1. Thus, Soreq et al. teach injecting mammalian subjects which have subjected to stress

with SEQ ID NO: 1 and thus said injection will inherently treat said stress or any other condition which has reduced lymphocyte activity such as chronic stress, autoimmune diseases, inflammation, rheumatoid arthritis, MS, amyotrophic lateral sclerosis, fibromyalgia, multiple chemical sensitivity, post-irradiation chemotherapy.

18. Claim 35 is rejected under 35 U.S.C. 102(b) as being anticipated by Soreq et al. (US 2003/0036632 – cited on IDS of 07-70-2008).

The claim is drawn to a method of inducing a shift in activity of lymphocytes *in vitro* or *ex vivo* by contacting an AChE-derived peptide with lymphocytes for a suitable period of time.

Soreq et al. teach the following: (see Example 4, paragraph 0288):

> [0288] In addition, the effect of ARP was examined in transformed bone marrow endothelial cells (Schweitzer et al, Lab Invest vol. 76, 5-36:1997). Cells were incubated in a serum free medium (SFM) with 2 nM of ARP, with or without endothelial growth factors (bFGF 20 ng/ml and EGF 10 ng/ml), for 48 hrs. As shown in FIG. 5, BrdU uptake increased in ARP presence. The effect was more pronounced when ARP was combined with bFGF and EGF.

It is well known in the art that bone marrow is the ultimate source of lymphocytes, thus the *in vitro* incubation of bone marrow cells with ARP (which is 100% identical to the instant SEQ ID NO: 1 as noted above) will induce a shift in the activity of said lymphocytes.

19. Claim 36 is rejected under 35 U.S.C. 102(b) as being anticipated by Soreq et al. (US 2003/0036632 – cited on IDS of 07-70-2008).

The claim is drawn to a method of detecting changes in activity of lymphocytes by measuring the expression of AChE-R on the surface of lymphocytes.

Soreq et al. teach the following (see Example 10, paragraph 0323):

> [0323] A series of AChE transgenic mouse pedigrees [Sternfeld et al. (1998b) id ibid.] was employed, to reveal if chronic increases in AChE-R would confer persistent changes in blood cell composition. Blood AChE levels, platelet and WBC counts were determined in FVB/N mice (Control, n=22) as compared to transgenic FVB/N mice carrying the AChE-S (TG-S, n=12), AChE-R (TG-R70 and TG-R45, n=9 and 6, respectively) or inert-inactivated AChE-S (AChE-Sin, n=3) transgenes. FIG. 12C shows results expressed as average+standard error of the mean (SEM). The transgenic lines expressing AChE-S variants indicated no increases in blood AChE and no significant deviations from a normal blood cell composition. In contrast, increases of 2.5 and 130-fold catalytic AChE activities were observed in two pedigrees (TG-R45 and TG-70R), whereas WBC counts were only increased in the more efficiently overproducing line, suggesting a gene dose dependent effect for ARP over the hematopoietic balance also under chronic excess conditions (FIG. 12C).

Thus, Soreq et al. teach measuring the expression of AChE-R in blood, wherein lymphocytes are known to be a type of white blood cell (e.g., the large granular cells are also known as natural killer cells (NK cells) and the small lymphocytes T or B cells). Thus, measuring the expression of said AChE-R in blood will inherently measure the expression derived from the expression of said AChE-R on the surface of lymphocytes.

In addition, Exmaple 2 (paragraphs 0279-0280) of Soreq et al. teach:

> [0279] The expression of ARP in CD34.sup.+ hematopoietic cells was evaluated by flow cytometry in whole cord blood **and bone marrow** from a patient with immune thrombocytopenic purpura (ITP), as demonstrated in FIG. 2A and FIG. 2B respectively. Bone marrow from ITP patients was chosen to study ARP expression in hematopoietic progenitor cells due to the high turnover of normal CD34.sup.+ in these patients. Cells were fixed and permeabiliazed with Fix and Perm (Caltag, Calif) and stained with moncoclonal antibodies to CD34 conjugated to pycoerythrin (Beckton Dickinson, Calif. indicated as FL-2 and with highly specific rabbit anti-ARP antibodies followed by anti rabbit antibodies conjugated to fluoroscein isothiocyanate, expression indicated as percentage of positive cells.

> [0280] These findings demonstrate higher expression of AChE-R in proliferating hematopoietic progenitors from either newborns or individuals suffering from over-proliferation of blood cells.

It is well known in the art that bone marrow is the ultimate source of lymphocytes, thus measuring the expression of AChE-R in said bone marrow will inherently measure the expression on the surface of said lymphocytes.

Conclusion

20. No claim is allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUZANNE M. NOAKES whose telephone number is (571)272-2924. The examiner can normally be reached on 7.00 AM-3.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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